Annals of Clinical and Analytical Medicine
Original Research

Effect of tocilizumab treatment on intubation and mortality rates in patients with severe COVID-19: A retrospective cross-sectional study

Kubilay Issever[1], Mehmet Emir Arman[2], Deniz Cekic[3], Ahmed Cihad Genc[4], Ahmed Bilal Genc[5], Ali Muhtaroglu[6], Selcuk Yaylaci[7]
[1] Department of Internal Medicine, Faculty of Medicine, Giresun University, Giresun
[2] Department of General Practitioner, Sakarya University Research and Educational Hospital, Sakarya
[3] Department of Internal Medicine, Sakarya University Research and Educational Hospital, Sakarya
[4] Department of Internal Medicine, Sakarya University Research and Educational Hospital, Sakarya
[5] Department of Internal Medicine, Faculty of Medicine, Sakarya University, Sakarya
[6] Department of General Surgery, Faculty of Medicine, Giresun University, Giresun
[7] Department of Internal Medicine, Faculty of Medicine, Sakarya University, Sakarya, Turkey

Abstract

Aim: COVID-19 has impacted all health facilities worldwide since 2020. Thus, finding curative treatments is vital, especially for patients with severe disease. In this study, we aimed to evaluate the curative potential of Tocilizumab in patients with severe COVID-19.

Material and Methods: Retrospectively, we analyzed the files of 154 patients treated in the intensive care units (ICU) between October 2020 and October 2021. Tocilizumab was administered to the patients before intubation as soon as the signs of the severe disease were noticed. The groups were compared as "tocilizumab" (Group T) vs. "non-tocilizumab" (Group NT).

Results: No significant age and gender differences were found between the tocilizumab and non-tocilizumab groups. Intubation (31.2% vs. 45.5%) and mortality rates (33.8% vs. 45.5%) were lower in the tocilizumab group, but the difference was not statistically significant ($p>0.05$). Group T was more frequently treated with glucocorticoids, while this group contained fewer patients with diabetes mellitus and chronic kidney failure ($p=0.01$ and 0.004, respectively). Correlation analysis revealed a slightly and moderately positive correlation of mortality and intubation with CPAP (Continuous Positive Airway Pressure) therapy, uric acid, AST (Aspartate Aminotransferase), creatine kinase (CK), lactate dehydrogenase (LDH), troponin I, Vitamin D, and interleukin-6 (IL-6) ($p=0.000$, 0.001, 0.032, 0.015, 0.000, 0.000, 0.004, and 0.002, respectively).

Discussion: Our results revealed that Tocilizumab might prevent intubation and death if administered early in patients with severe COVID-19.

Keywords

Tocilizumab, COVID-19, Mortality, Intubation

DOI: 10.4328/ACAM.21833 Received: 2023-07-27 Accepted: 2023-08-28 Published Online: 2023-09-06 Printed: 2023-09-25 Ann Clin Anal Med 2023;14(Suppl 2):S140-145
Corresponding Author: Kubilay Issever, Department of Internal Medicine, Faculty of Medicine, Giresun University, Merkez, Giresun, Turkey.
E-mail: kubilayissever@gmail.com P: +90 531 381 74 75
Corresponding Author ORCID ID: https://orcid.org/0000-0002-1376-1488
This study was approved by the Ethics Committee of Sakarya University Medical Faculty (Date: 2021-05-29, No: E-71522473-050.01.04-32203-320)

Introduction

A novel Coronavirus disease caused by SARS-CoV-2 was first detected in China in December 2019 and has become a pandemic causing the fatality of millions of people so far. Thousands of studies have revealed that this disease might affect any body part, but severe disease is almost always associated with respiratory tract infection [1]. A relevant part of the infected patients might present with acute respiratory distress syndrome (ARDS) and should be treated in ICUs [1]. Since evolving data reported high mortality rates for intubated patients, delaying or avoiding intubation as much as possible with non-invasive mechanical ventilation (NIMV) methods such as high-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP), especially with prone positioning, has been the management of choice for a long time for patients with severe respiratory failure [2]. Besides NIMV, treatment options that have been shown to avoid intubation would also reduce mortality rates due to this known fact. Remdesivir, dexamethasone, tocilizumab, baricitinib, and molnupiravir are in the frame of these treatments that show promising results [3]. Besides, tocilizumab is one of the most recommended drugs by the guidelines for severe COVID-19, along with dexamethasone [3,4].

Macrophage activation syndrome (MAS) is a dysfunctional, unproportional, exacerbated immune response to a pathogen or triggered by an autoimmune process. Cytokines and chemokines such as interleukin-1, interleukin-6, tumor necrosis factor-alfa, and interferon-gamma have been found to be triggered and activated significantly by SARS-CoV-2 in some patients [5]. The term "cytokine storm" can also describe this "cytokine madness." MAS can cause acute respiratory distress (ARDS) and multiple organ failure. ARDS in severe COVID-19 can be described as hypoxic respiratory failure and is characterized by microvascular thrombosis, diffuse alveolar damage, and myeloid cell infiltrates [4]. Considering this pathophysiology underlying severe COVID-19, researchers focused on immunosuppressive agents to modify or control this hyperinflammatory state. Following the presentation of promising results from the dexamethasone study, immunomodulatory agents were the best candidates to prevent intubation and mortality in these patients [4].

As an immunomodulatory agent, Tocilizumab can reduce inflammation by inhibiting the binding of IL-6 to both membrane and soluble IL-6 receptors, thus blocking IL-6 signaling [4]. Tocilizumab can be used to treat not only rheumatoid arthritis but also giant-cell arthritis, systemic sclerosis, and juvenile idiopathic arthritis [6]. While the use of tocilizumab in patients with severe COVID-19 appears to be a logical hypothesis, clinical trials have revealed controversial results so far. Eight guidelines recommended its use in combination with dexamethasone in patients with severe disease whereas seven small trials reported no benefit in addition to a larger trial reporting a benefit only in patients requiring organ support [3]. These controversial results reveal that the literature still needs more studies to determine whether tocilizumab is effective in COVID-19 patients. Considering this fact, we aimed to analyze the effect of tocilizumab in patients with severe COVID-19 in this study.

Material and Methods

Our study was a retrospective cross-sectional study. The study included one hundred fifty-four patients treated in the Sakarya University Training and Research Hospital ICUs. This study was approved by Sakarya University Medical Faculty Ethical Committee (27/04/2020-E.4266). (Date: May 29, 2021, File number: E-71522473-050.01.04-32203-320). The authors have complied with the international guidelines, the "Regulations on Pharmaceutical Research," enforced by The Ministry of Health of Turkey published in the 27089 numbered Official Journal dated 23 December 2008 and also with other regulations published at a later date.

Nasopharyngeal swab PCR test positivity was accepted as the gold standard for diagnosing COVID-19. Patients who were below the age of 18 and had negative PCR test results were excluded from the study.

During the first year of the pandemic, the standard treatment protocol in our institution for a patient with severe COVID-19 was favipiravir for 5 to 10 days (2x1600mg as loading dose, 2x600mg as maintenance dose) plus dexamethasone 24 mg IV for the first three days, 16 mg IV for the second three days and 8 mg IV for the third three days (or methylprednisolone ≥ 250 mg IV for the first three days, 80-250 mg IV for the second three days, and 80 mg IV for the third three days). After nine days, tapering the dexamethasone or methylprednisolone dose daily to prevent adrenal insufficiency, irrespective of the patient's clinical status, was also part of our medical protocol. All patients included in the study were treated with this protocol during the first year of the pandemic. Standard Iv fluid resuscitation, anti biotherapy (if needed), standard oxygen support (nasal cannula, non-rebreather mask, HFNC, CPAP, intubation, respectively), prone positioning (PP) up to 16 hours if tolerated, low molecular weight heparin as an anticoagulant, proton pump inhibitors for stress ulcer prophylaxis were also part of the standard ICU treatment protocols for these patients. However, following the emerging studies suggesting the possible beneficial effects of tocilizumab in COVID-19 patients, the Ministry of Health started to provide tocilizumab only for a particular group of patients in the second year of the pandemic. Patients under 65 years of age who were in MAS were the candidates for tocilizumab treatment. Clinical findings associated with MAS were defined as ongoing resistant fever, constantly elevated or increasing levels of C-reactive protein (CRP), constantly elevated or increasing levels of ferritin (> 700 µg/L), elevated D-dimer levels, lymphopenia, thrombocytopenia, neutrophilia, and elevated liver enzymes in the guideline of the ministry of health. Patients who received or did not receive tocilizumab therapy were chosen randomly from the medical files except for the age and gender matching. We defined patients who received tocilizumab treatment at any time of their ICU stay as the "tocilizumab group" (T) and patients who received standard therapy as the "non-tocilizumab group" (NT). Demographic, laboratory, and clinical parameters were compared between these groups. Laboratory parameters obtained at the time of admission to the ICU were used for analysis. The collected data were analyzed in the biostatistical program.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics package program.

The suitability of the patients' numerical variables to the normal distribution was determined by looking at the skewness values. Only the values of Albumin, LDH, Fibrinogen, HB, and PLT of the patients corresponded to normal distribution rules. The reference value in the normal distribution is between ±1.5 7]. The chi-square test was used to compare the introductory characteristics of the patients, their use of various drugs, and the findings of comorbidities according to their tocilizumab drug use and discharge status. The Independent Sample T Test or Mann Whitney U test was used to compare laboratory parameters according to tocilizumab drug use and discharge status. Pearson or Spearman Correlation tests were used to examine the relationships between tocilizumab use, mortality, intubation status, and parameters. Correlation coefficient; A relationship between 0.00-0.30 was considered as low, between 0.30-0.70 as a medium level, and between 0.70-1.00 as a high-level relationship [8]. Logistic regression analysis was applied to estimate the mortality and intubation probability of the patients. The significance levels were carried out in the study considering the 0.05 and 0.01.[7]. The chi-square test was used to compare the introductory characteristics of the patients, their use of various drugs, and the findings of comorbidities according to their tocilizumab drug use and discharge status. The Independent Sample T- test or Mann-Whitney U test was used to compare laboratory parameters according to tocilizumab drug use and discharge status. Pearson's or Spearman' Correlation tests were used to examine the relationships between tocilizumab use, mortality, intubation status, and parameters. Correlation coefficient: a relationship between 0.00-0.30 was considered as low, between 0.30-0.70 as a medium level, and between 0.70-1.00 as a high-level relationship [8]. Logistic regression analysis was applied to estimate the mortality and intubation probability of the patients. The significance levels were carried out in the study considering the 0.05 and 0.01.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

There was no statistical age or gender difference between the groups. The median age was 55 for the non-tocilizumab group and 52 for the tocilizumab group. HFNC therapy was more frequently applied in group T (p=0.000). Although CPAP therapy was also more frequently applied in Group T (31.2% vs. 23.4%), the difference could not reach a statistically significant level. Patients in Group NT had higher intubation (45.5% vs. 31.2%) and mortality (45.5% vs. 33.8%) rates; however, these differences were not statistically significant. The average day after intubation was approximately 4.2 for Group NT and 2.2 for Group T. This difference was also insignificant Table 1 showsthat significantly more patients received dexamethasone 8 mg, methylprednisolone 80-250 mg, and methylprednisolone <80 mg in Group T (p=0.000, 0.026, and 0.02, respectively). In contrast, more patients in Group NT received plasmapheresis and convalescent plasma therapy (p=0.004 and 0.019, respectively). Significantly more patients in the NT group had DM and CRF as comorbidities (p=0.01 and 0.004, respectively). Other treatment modalities and comorbidities did not differ significantly between the groups (Table 1).

Laboratory parameters were analyzed and compared between the groups in Table 2. Patients in Group T had significantly higher levels of aspartate aminotransferase (AST), albumin, myoglobin, and Vitamin D (p=0.024, 0.000, 0.000, and 0.023, respectively), whereas lower levels of uric acid, troponin, and lymphocyte (p=0.037, 0.012, and 0.008, respectively). No other significant difference was found regarding lab parameters between the groups (Table 2).

Table 3 demonstrates the correlation of mortality and intubation rates with the factors affecting these rates. As expected, a strong positive correlation was determined between mortality and intubation rates and duration (p=0.000 for both). Slightly and moderately positive correlation was found between

Table 1. Comparison of the groups regarding other applied treatments for COVID-19 and comorbidities.

Treatments and comorbidities		Group NT (n:77)		Group T (n:77)		p
		N	%	n	%	
Dexamethasone 8 mg	No	40	51.9	9	11.7	<0,001**
	Yes	37	48.1	68	88.3	
Methylprednisolone> 250 mg	No	55	73.3	56	72.7	0.933
	Yes	20	26.7	21	27.3	
Methylprednisolone 80-250 mg	No	64	85.3	53	68.8	0.026*
	Yes	11	14.7	24	31.2	
Methylprednsolone <80 mg	No	66	88.0	55	71.4	0.02*
	Yes	9	12.0	22	28.6	
IVIG	No	68	90.7	75	97.4	0.157
	Yes	7	9.3	2	2.6	
Favipiravir	No	3	3.9	4	5.2	1.000
	Yes	74	96.1	73	94.8	
Plasmapheresis	No	65	84.4	76	98.7	0.004**
	Yes	12	15.6	1	1.3	
C. Plasma	No	61	79.2	72	93.5	0.019*
	Yes	16	20.8	5	6.5	
DM	No	54	70.1	68	88.3	0.01*
	Yes	23	29.9	9	11.7	
HT	No	48	62.3	54	70.1	0.394
	Yes	29	37.7	23	29.9	
CAD	No	65	84.4	69	89.6	0.472
	Yes	12	15.6	8	10.4	
COPD	No	72	93.5	76	98.7	0.212
	Yes	5	6.5	1	1.3	
CRF	No	65	84.4	76	98.7	0.004**
	Yes	12	15.6	1	1.3	
HBV	No	75	97.4	77	100.0	0.477
	Yes	2	2.6	0	0.0	
Malignancy	No	73	94.8	74	96.1	1.000
	Yes	4	5.2	3	3.9	
Neurological Diseases	No	72	93.5	75	97.4	0.439
	Yes	5	6.5	2	2.6	
AF	No	76	98.7	75	97.4	1.000
	Yes	1	1.3	2	2.6	
Others	No	65	84.4	54	70.1	0.054
	Yes	12	15.6	23	29.9	

*p<0,05, **p<0,01, x^2: Chi-square test, IVIG: Intravenous Immunoglobulin, C. Plasma: Convalescent Plasma, DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, CRF: Chronic Renal Failure, HBV: Hepatitis B Virus, AF: Atrial Fibrillation,

Table 2. Comparison of the laboratory parameters between the groups.

Lab parameters	Group NT (n:77)	Group T (n:77)	p
	Med.±S.D. (Min.-Max.)	Med.±S.D. (Min.-Max.)	
FBG[z]	185.88±97.86 154 (73-498)	169.06±62.54 151 (80-400)	0.894
Uric Acid[z]	5.46±2.43 4.60 (2,10-15)	4.67±2.00 4.20 (1.80-14.00)	0.037*
ALT[z]	45.62±44.30 32 (5-292)	51.91±39.57 41 (7-199)	0.088
AST[z]	52.57±50.00 39 (14-286)	57.57±36.40 50 (15-248)	0.024*
Albumin[t]	3.01±0.61	3.31±0.33	<0.001**
CK[z]	252.02±535.29 90 (9-2193)	283.91±542.17 117.5 (18-3503)	0.388
LDH[t]	566.38±290.48	603.91±214.53	0.365
Ferritin[z]	1228.67±1423.19 790 (1.90-8.206)	1225.52±1095.03 801.22 (59.28-4955)	0.295
Troponin I[z]	48.99±137.84 9.00 (0.80-900)	44.61±256.08 6.10 (0,60-2152)	0.012*
Myoglobin[z]	24.82±13.41 29 (2-53)	134.57±181.46 76.85 (2,20-1200)	<0.001**
Fibrinogen[t]	459.11±159.19	482.58±143.81	0.343
D-dimer[z]	582.90±470.45 (453-110)	676.71±403.29 562 (110-2050)	0.054
Vitamin D[z]	12.90±7.35 11.70 (4.00-34.10)	20.39±13.85 14.79 (7.47-62.67)	0.023*
IL-6[z]	152.64±194.01 46.47 (1.50-640)	83.74±187.46 34.63 (1.50-1401)	0.397
CRP[z]	121.09±100.93 103.00 (3.00-640)	115.15±65.04 111 (7.17-313)	0.648
WBC[z]	10.50±6.35 8.95 (2.98-38)	10.69±7.56 9.66 (1.78-48.80)	0.826
HB[t]	11.96±2.24	11.96±1.56	0.992
PLT[t]	223.97±106.41	233.86±95.78	0.545
Neutrophil[z]	8.98±5.77 7.60 (2.10-32.40)	9.91±6.81 9.00 (1.20-44.42)	0.318
Lymphocyte[z]	0.95±0.94 0.78 (0.11-6.56)	0.65±0.42 0.52 (0.00-1.99)	0.008**

*p<0,05, **p<0,01, t: Independent Sample T-test, z: Mann-Whitney U test, Med: Median, S.D.:Standard Deviation, Min: Minimum, Max: Maximum, FBG: Fasting Blood Glucose, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, CK: Creatine Kinase, LDH: Lactate Dehydrogenase, IL-6:Interleukin-6, CRP: C-Reactive Protein, WBC: White Blood Cell, HB:Hemoglobin, PLT: Platelets

Table 3. Correlation analysis of mortality and intubation rates with other variables.

Variables	Co-Effic.	Mortality	Intubation
Mortality	r	1	.837**
	p	.	<0.001
Intubation	r	.837**	1
	p	<0.001	.
Intubation Duration	r	.780**	.963**
	p	<0.001	<0.001
CPAP	r	.309**	.297**
	p	<0.001	<0.001
Uric Acid	r	.274**	.214**
	p	0.001	0.008
AST	r	.173*	.195*
	p	0.032	0.015
Albumin	r	-0.143	-.258**
	p	0.077	0.001
CK	r	.212*	.196*
	p	0.015	0.025
LDH	r	.280**	.203*
	p	<0.001	0.012
Troponin	r	.298**	.279**
	p	<0.001	0.001
Vitamin D	r	.365**	.298*
	p	0.004	0.019
IL-6	r	.327**	.302**
	p	0.002	0.005

*p<0,05, **p<0,01, r: Correlation Coefficient, Co-Effic: Coefficient

mortality and CPAP therapy, uric acid, AST, creatine kinase (CK), lactate dehydrogenase (LDH), troponin, Vitamin D, and interleukin-6 (IL-6) (p=0.000, 0.001, 0.032, 0.015, 0.000, 0.000, 0.004, and 0.002, respectively). Slightly and moderately positive correlation was found between intubation and CPAP therapy, uric acid, AST, CK, LDH, troponin, Vitamin D, and IL-6 (p=0.000, 0.008, 0.015, 0.025, 0.012, 0.001, 0.012, and 0.019, respectively). A slightly negative correlation was found between intubation and albumin levels (p=0.001) (Table 3).

Discussion

The results of our study revealed that Tocilizumab might be effective not only in reducing the risk of death but also in preventing intubation in patients with severe COVID-19. Although the difference between these groups seems insignificant statistically, the percentage difference is noticeable (31.2% vs. 45.5% for intubation and 33.8% vs. 45.5% for mortality). As authors, we are sure that the difference would be statistically significant if the number of patients were higher. This result is important when considering the literature's disagreement regarding this agent's benefit in COVID-19 patients. These kinds of studies are also critical for determining the place of immunomodulatory agents in treating autoimmune and infectious diseases, which can progress to cytokine storm and ARDS during their clinical courses. The agents that were shown to be effective against COVID-19 can also be used in future pandemics if the causative virus shows similar characteristics to SARS-CoV-2.

Stone et al. reported no benefit of Tocilizumab in their

randomized-controlled trial (RCT) of 243 moderately ill COVID-19 patients [9]. Similarly, a phase 3 trial including 452 severe COVID-19 patients did not result in significantly better clinical status or lower mortality than the placebo at 28 days [10]. Another randomised-controlled phase 3 trial revealed that Sarilumab (an interleukin-6 antagonist similar to Tocilizumab) does not have an efficacy in hospitalized COVID-19 patients receiving supplemental oxygen [11]. Despite these heartbreaking results, most of the studies in the literature reported promising results for using IL-6 antagonists in COVID-19. The first results of the randomized controlled study that the RECOVERY Collaborative Group started in April 2020 suggested a beneficial effect of Tocilizumab in hospitalized COVID-19 patients with hypoxia and systemic inflammation when combined with systemic corticosteroids [12]. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group evaluated the place of IL-6 antagonists such as tocilizumab, sarilumab, and siltuximab in COVID-19 in their meta-analysis consisting of 27 trials and 10930 patients. This study showed that administration of IL-6 antagonists, compared with placebo or usual care, was associated with lower 28-day all-cause mortality [13]. Similarly, in a review that evaluated the recommendations of clinical guidelines for COVID-19, 10 of 12 guidelines recommended the use of tocilizumab in severe disease. Eight of these ten guidelines recommended its use combined with dexamethasone [3]. In a multicenter cohort study that included 3924 patients with severe COVID-19, the risk of in-hospital death was estimated to be lower with early tocilizumab treatment compared with no use of early tocilizumab 14]. [14].

Remarkably, most studies suggesting the beneficial effects of tocilizumab agree on its use in combination with dexamethasone and for patients, especially with severe disease. Table 2 reveals that more patients in group T received glucocorticoids during their treatments. While analyzing the results, it is vital to remember that group NT consisted of the patients treated in the first months of the pandemic, while group T contained patients from later phases. Thus, this difference can be explained by the late introduction of steroid treatment for severe COVID-19 and the strong recommendation of combination therapy by guidelines. Commonly usage of convalescent plasma therapy and plasmapheresis might also be explained by their experimental application during the first phases of the pandemic.

Our results reveal that tocilizumab might prevent intubation in patients with severe COVID-19. These results were in the same line with most of the reports in the literature. Arthur et al. reported a significant reduction in the need for mechanical ventilation in their review, analyzing the results of 10 RCTs [15]. Even in the phase 3 trial, which reported no beneficial effect of tocilizumab in COVID, as we mentioned above, ventilator-free days were 22 in the tocilizumab group, whereas it was 16 for the control group [10]. As a game-changer study for the treatment of COVID-19, the study of the RECOVERY group also reported a reduced intubation rate in the tocilizumab group [12]. However, in the study, Stone et al. conducted, the need for mechanical ventilation or death before intubation was similar between tocilizumab and the control group [9]. The potential reasons behind the increased incidence of HFNC therapy application in group T were the increased frequency of HFNC application in the later phases of the pandemic and the higher application rate of the tocilizumab to the patients with the severe disease before the intubation in which NIMV techniques are highly used. Considering the positive correlation between comorbidities and mortality in patients with severe COVID-19, it was unsurprising to determine a higher incidence of CRF and DM in the group NT since this group had a higher mortality rate. 0]. As a game-changer study for the treatment of COVID-19, the study of the RECOVERY group also reported a reduced intubation rate in the tocilizumab group [12]. However, in the study by Stone et al., the need for mechanical ventilation or death before intubation was similar between tocilizumab and the control group [9]. The potential reasons behind the increased incidence of HFNC therapy application in group T were the increased frequency of HFNC application in the later phases of the pandemic and the higher application rate of the tocilizumab to the patients with the severe disease before the intubation in which NIMV techniques are highly used. Considering the positive correlation between comorbidities and mortality in patients with severe COVID-19, it was unsurprising to determine a higher incidence of CRF and DM in the NT group since this group had a higher mortality rate.

We compared the laboratory data between the groups in Table 3. Albumin, vitamin D, AST, and myoglobin levels were significantly higher in the T group. In contrast, uric acid, troponin I, and lymphocyte levels were significantly higher in the NT group. In this study, we chose the control group of similar age and gender as the patient group to rule out the mortality effects of these parameters. Nevertheless, laboratory parameters that are famously known to be associated with mortality in COVID-19, such as higher uric acid and troponin I, lower albumin, and vitamin D, were more frequently seen in the NT group [12,16,17,18]. These findings were compatible with the higher mortality rate in the NT group. Exceptional laboratory parameters at this point are the lymphocyte count, AST, and myoglobin. Lower lymphocyte levels are associated with an increased risk of death in COVID-19; however, higher levels of this parameter were found in the NT group, which is a more mortal group. Likewise, myoglobin and AST levels are reported to be associated with higher mortality in severe COVID-19 in the literature, although they were detected at higher levels in the T group, where the mortality rate was lower. Surprisingly, the levels of some laboratory parameters reported as mortality biomarkers in COVID-19 so far in the literature, such as CK, CRP, IL-6, platelets, ferritin, neutrophile count, D-dimer, fibrinogen, and LDH, did not differ significantly between the groups. Especially the similarity between the groups regarding acute phase reactants such as IL-6, CRP, and ferritin showed us that the clinical severity of the patients included in the study was close to each other. This characteristic of the groups can be considered as a healthy sign of objective comparison between the groups.

Analyses evaluating the correlation levels of some significant parameters with mortality and intubation revealed a slightly and moderately positive correlation with CPAP therapy, uric acid, AST, CK, LDH, troponin, Vitamin D, and IL-6. These results were compatible with the literature since these parameters

were reported to be associated with increased mortality and intubation rates. The only exceptional parameter is vitamin D since its lower levels are generally associated with higher mortality and intubation rate in COVID-19 patients [19].

Limitations

Our study has some limitations. It was a retrospective study with a small patient group. Additionally, patients receiving different therapies could not be distinguished and presented in small groups for subgroup analysis. Finally, it would be better to obtain the patients' laboratory test results and follow-up data after the treatments and compare them as "before vs. after". Despite these limitations, our study could contribute to the "controversial" literature regarding the beneficial effects of tocilizumab.

Tocilizumab can prevent intubation and death if administered early in patients with severe COVID-19. More randomized controlled studies with larger patient populations are needed to better clarify the effect of tocilizumab treatment on COVID-19 patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding: *None*

Conflict of interest

The authors declare no conflict of interest.

References

1. Yang X, Yu Y, Xu J, Shu H, Xia J 'an, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.

2. Arulkumaran N, Brealey D, Howell D, Singer M. Use of non-invasive ventilation for patients with COVID-19: a cause for concern? Lancet Respir Med. 2020;8(6):e45.

3. Wohl DA, Espinueva AA, Dau L, Wang CY, Lachmann A, Bam RA, et al. COVID-19 therapies for inpatients: a review and quality assessment of clinical guidelines. ERJ Open Res. 2022;8(4):00236-2022.

4. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704.

5. Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. Inflamm Regen. 2020;40:19.

6. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (Actemra). Hum Vaccin Immunother. 2017;13(9):1972-88.

7. Tabachnick BG, Fidell LS. Using Multivariate Statistics, 6th ed. Boston, MA: Pearson; 2013. p.1060.

8. Bütüner SÖ, Büyüköztürk Ş, editors. Sosyal Bilimler için Veri Analizi El Kitabı [Handbook of Data Analysis for Social Sciences]. Ankara: Pegem A. Publishing; 2008. p.6-8.

9. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333-44.

10. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021;384(16):1503-16.

11. Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(5):522-32.

12. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.

13. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Domingo P, Mur I, Mateo GM, del Mar Gutierrez M, Pomar V, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021;326(6):499-518.

14. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. 2021;181(1):41-51.

15. Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran N. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med. 2021;47(6):641-52.

16. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-8.

17. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med. 2020;144(12):1465-74.

18. Wei T, Li J, Cheng Z, Jiang L, Zhang J, Wang H, et al. Hematological characteristics of COVID-19 patients with fever infected by the Omicron variant in Shanghai: A retrospective cohort study in China. J Clin Lab Anal. 2023;37(1):e24808.

19. Trovas G, Tournis S. Vitamin D and COVID-19. Hormones (Athens). 2021;20(1):207-8.

How to cite this article:

Kubilay Issever, Mehmet Emir Arman, Deniz Cekic, Ahmed Cihad Genc, Ahmed Bilal Genc, Ali Muhtaroglu, Selcuk Yaylaci. *Effect of tocilizumab treatment on intubation and mortality rates in patients with severe COVID-19: A retrospective cross-sectional study. Ann Clin Anal Med 2023;14(Suppl 2):S140-145*

This study was approved by the Ethics Committee of Sakarya University Medical Faculty (Date: 2021-05-29, No: E-71522473-050.01.04-32203-320)